REMARKS

Amendments

The Claims are amended to recite an inherent feature, that the targeted PAS domain is selected and folded, and to cancel the functional equivalent but perhaps less clear "predetermined, prefolded" language. These amendments do not alter the scope or meaning of the Specification and Claims and introduce no new matter.

Abstract

We believe the abstract, though a long sentence, is grammatically correct as presented. Relieved of several prepositional phrases and a wherein clause, the Abstract reads as follows: A functional surface binding specificity is changed by (a) introducing a foreign ligand; and (b) detecting a change in the functional surface binding specificity.

Specification-Objections

The Specification includes a required "BRIEF" description of the drawings section at p.3-4; and more extensive descriptions of the same figures are provided at p.26-27.

No other drawings or flow diagrams are present in this application, but only three tables of chemical structures and related text at p. 28-31. Chemical structures are permitted in the specification (see e.g. 37 CFR 1.52 (b)(6): Non-text elements (e.g., tables, mathematical or chemical formulae, chemical structures, and sequence data) are considered part of the numbered paragraph...).

Double Patenting

Upon allowance of an overlapping claim in the cited 10/677,733 application, a terminal disclaimer will be filed.

35USC112, second paragraph

The clarity issues are believed avoided by the foregoing amendments.

35USC112, first paragraph (enablement)

The claims are directed to a method of changing a functional surface binding specificity of a selected PAS domain by (a) introducing into the hydrophobic core of the PAS domain a

foreign ligand of the PAS domain; and (b) detecting a resultant change in the functional surface binding specificity of the PAS domain, *wherein the PAS domain is HIF2a PAS B....*

Hence, the claimed method is not open to using any PAS domain of any structure, but is limited to the use of a particular PAS domain: the HIF2a PAS B domain. This is an art-recognized, defined protein domain -- there are hundreds of scientific publications describing the HIF2a PAS B domain, and how to use it. One skilled in the art does not require undue effort or experimentation to recognize and procure an HIF2a PAS B domain for use in the claimed methods. See attached expert Declaration under 37CFR1.132.

35USC112, first paragraph (written description)

The claims are directed to a method of changing a functional surface binding specificity of a selected PAS domain by (a) introducing into the hydrophobic core of the PAS domain a foreign ligand of the PAS domain; and (b) detecting a resultant change in the functional surface binding specificity of the PAS domain, *wherein the PAS domain is HIF2a PAS B....*

Hence, the claimed method is not open to using any PAS domain of any structure, but is limited to the use of a particular PAS domain: the HIF2a PAS B domain. This is an art-recognized, defined protein domain -- there are hundreds of scientific publications describing the HIF2a PAS B domain, and how to use it. One skilled in the art has no trouble recognizing an HIF2a PAS B domain for use in the claimed methods. See attached expert Declaration under 37CFR1.132.

35USC103(a)

The claims are directed to a method of changing a functional surface binding specificity of a selected PAS domain, wherein the PAS domain is folded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity by (a) introducing into the hydrophobic core of the PAS domain a foreign ligand of the PAS domain; and (b) detecting a resultant change in the functional surface binding specificity of the PAS domain, wherein the PAS domain is HIF2a PAS B, and the binding specificity is a change in intramolecular binding affinity of the PAS domain detected as a change in chemical shifts detected by 1H/15N-HSQC NMR....

Vogtherr (2003) generally describes the use of NMR-based screening for lead discovery; Amexcua (2002) describes the used of NMR to detect ligand binding to PAS kinase; Ema (1997)

reports that *HIF1a* heterodimerizes with Arnt (note that HIF1a is structurally and functionally distinct from the recited HIF2a; Sowter 2003, attached); and Fukunaga (1995) reports identification of functional domains of the aryl hydrocarbon receptor.

Prior to the present disclosure, HIF was known to be regulated in several ways by oxygen availability, but via non-PAS mediated mechanisms only (CITES), which taught away from any expectation that the HIF PAS domains would be sensory. In addition, HIF2a PASB presents a well-folded domain lacking the dynamic regions of PASK PAS A and long insertion loops of NPAS2 PAS A (Erbel et al., 2003, attached), further removing any expectation of core ligand binding.

As explained in our Specification some members of the PAS family (e.g. aryl hydrocarbon receptor) are known to contain small molecule cofactors within their cores, and these cofactors are reportedly required for proper folding and functioning of the PAS domain within the context of the holo-protein. Specification, p.1, line 22 - p.2, line 1. However, for most PAS domains, including HIF2a PASB, there is no evidence for such a cofactor. In fact, such structurally characterized PAS domains without bound cofactors (Amezcua et al., 2002; Erbel et al., 2003; Morais Cabral et al., 1998) show tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site. Specification, p.2, lines 2-5. Since the prior work provided no evidence of cofactors for most PAS domains, including HIF2a PASB, and taught that those limited PAS domains having cofactors required them for proper folding, and taught that PAS domains without cofactors had tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site, one skilled in the art would not have suspected such PAS domains to provide a core for sensory ligand binding.

Attached is an expert Declaration confirming that one skilled in the art at the time of our filing would not have expected HIF2a PAS to provide a core for sensory ligand binding.

The Examiner is invited to call the undersigned with any suggestions for amending the claims or further clarifying any of the foregoing. Please charge any required fees, including extension fees, or credit any overcharges relating to this communication to our Dep. Acct. No.19-0750 (order UTSD:1510-1).

Respectfully submitted,
Science & Technology Law Group

Richard Aron Osman, J.D., Ph.D., Reg. No. 36,627
Tel (949) 218-1757; Fax (949) 218-1767

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Encl. Erbel et al., 2003, Proc Natl Acad Sci USA 2003 Dec 23;100(26):15504-9.
Sowter et al., 2003, Cancer Res. 2003 Oct 1;63(19):6130-4.
Declaration under 37CFR1.132